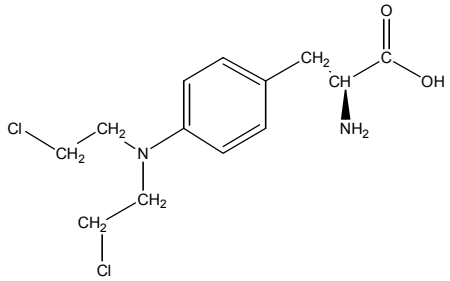
MELPHALAN
CAS No. 148-82-3
First Listed in the *First Annual Report on Carcinogens*



CARCINOGENICITY

Melphalan is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC S.4, 1982; IARC S.7, 1987). Epidemiological studies showed substantially increased rates of leukemia in patients treated with melphalan for breast cancer, ovarian cancer, and multiple myeloma. The relative risk was consistently estimated to be in excess of 100, to increase with increasing dose, and to be roughly the same with and without radiotherapy.

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of melphalan in experimental animals (IARC V.9, 1975, IARC S.4, 1982; IARC S.7, 1987). When administered by intraperitoneal injection, melphalan induced lymphosarcomas in male mice, lung tumors in mice of both sexes, and peritoneal sarcomas in rats of both sexes.

PROPERTIES

Melphalan is a white, odorless powder that is practically insoluble in water but is subject to rapid hydrolysis in water and plasma. It is soluble in ethanol, propylene glycol, alkaline solution, 2% carboxymethylcellulose, and dilute mineral acid. When heated to decomposition, it emits toxic fumes of hydrochloric acid and other chlorinated compounds as well as nitrogen oxides (NO_x). Melphalan USP-grade powder, used to formulate tablets, contains 93.0%-100.5% melphalan.

USE

Melphalan is used to treat multiple myeloma and cancer of the ovary and in investigations of other types of cancer. It also is used as an antineoplastic agent in animals (IARC V.9, 1975).

PRODUCTION

Melphalan is not currently produced in the United States, and only one domestic supplier has been reported (SRIa, 1986; HSDB, 1997). The USITC reports that 1983 imports of melphalan totaled 363 lb (USTICa, 1984; HSDB, 1997), compared with an estimated 3,000 lb imported in 1977 (TSCA, 1979). No data on exports were available.

EXPOSURE

The primary routes of potential human exposure to melphalan are ingestion, injection, inhalation, and dermal contact. FDA estimates that 30,000 to 50,000 patients may be treated for cancer with melphalan each year. Melphalan is administered orally or intravenously, at a dose rate of 2 to 15 mg daily for a period of 2 or 3 weeks (IARC V.9, 1975). Health professionals (e.g., pharmacists, nurses, and physicians) involved in cancer chemotherapy possibly may be exposed to melphalan. This exposure may occur during drug preparation, administration, or cleanup; however, the risks can be avoided through use of appropriate containment equipment and work practices (Zimmerman et al., 1981). A recent investigation has found that the exposure of hospital personnel to melphalan can be reduced by treating excess solutions, spills, and urinals with chlorine bleach (sodium hypochlorite, NaOCl, at 5.25%). No mutagenic residues are generated by the treatment, and complete degradation occurs in one hour (Hansel et al., 1997). Potential occupational exposure may also occur for workers involved in the formulation and packaging of the pharmaceuticals. The National Occupational Exposure Survey (1981-1983) estimated that 2,416 total workers, including 975 women, were potentially occupationally exposed to melphalan (NIOSH, 1984).

REGULATIONS

EPA regulates melphalan under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA). A reportable quantity (RQ) of 1 lb has been established for melphalan under CERCLA. It is listed as a hazardous constituent of waste and is regulated under the hazardous waste disposal rule of RCRA. FDA has approved melphalan for treatment of myeloma and epithelial ovarian cancer under the Food, Drug, and Cosmetic Act (FD&CA). Melphalan is subject to labeling requirements for potential carcinogenicity, mutagenicity, teratogenicity, and/or fertility impairment under FD&CA. OSHA regulates melphalan under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table A-28.